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(54) Title: NUTRIENT SUPPLY

(57) Abstract

The invention relates to a composition for oral or parenteral use, characterized in that the composition contains free L-glutamine and also at least one derivative of L-glutamine and optionally at least one precursor to L-glutamine, the composition being prepared aseptically and freeze-dried in powder form and radiation-sterilized, or in the form of a solution which is stored at low temperature, preferably in deep-frozen form. The derivative preferably consists of peptides, such as glycyl-L-glutamine and/or L-alanyl-L-glutamine, and the precursor may consist of alpha-keto-glutaric acid or the salt/derivative thereof. The derivative may also consist of N-acetyl-L-glutamine. The composition may also contain other nutrient components, or technical auxiliary substances, such as carbohydrates, sugar alcohols, vitamins and/or amino acids, preferably in freeze-dried form. The invention also relates to the production of the composition and to a method of preparing a nutrient solution.

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# NUTRIENT SUPPLY

The present invention relates to a preparation which makes possible the parenteral or oral administration of a balanced nutrient solution containing a high concentration of glutamine and glutamine derivative or glutamine precursors.

More specifically, but not exclusively, the invention relates to a preparation which contains L-glutamine and also at least one glutamine derivative, preferably glycyl-L-glutamine and/or L-alanyl-L-glutamine or a precursor of L-glutamine, preferably alpha-keto-glutaric acid and salts/derivatives thereof. N-acetyl-L-glutamine can also be used.

The invention also relates to a nutrient solution and to a method of preparing the same, said solution optionally containing such nutrients as amino acids, fats, particularly emulsified fats, energy substrates, such as glucose, sugar alcohols and keto-acids, electrolytes, vitamins and trace elements.

## Background

Intravenous nutrient therapy has become progressively more complete and better balanced as the significance of new substances, or the significance of substances which have earlier been overlooked, has become more apparent.

Observations made in recent years have shown that glutamine is highly significant when used as a component of nutrient support compositions. In the metabolic circulation of nitrogen, glutamine is the most significant transporter by means of which nitrogen is transported

from muscle to intestines and liver. According to certain theories, glutamine has a stimulating effect on the synthesis of proteins in muscle tissue. The store of free glutamine in skeletal muscle diminishes drastically in patients who have suffered serious trauma, surgical operations, sepsis, etc. (Vinnars E., Bergström, and Fürst, P.: Influence of the Postoperative State on the Intracellular Free Amino Acids in Human Muscle Tissue; Annals of Surgery 182:665-671 (1975) and Askanazi, J., et al: Muscle and Plasma Amino Acids Follow Injury. Influence of Intercurrent Infection. Ann Surg. 192:78-85 (1980).

Glutamine also constitutes an essential energy source for the intestinal mucus membrane (Windmueller, H.G., Spaeth, A.E.: Identification of Ketone Bodies and Glutamine as the Major Respiratory Fuels in Vivo for Postabsorptive Rat Small Intestine, J. Biol. Chem. 253:69-76 (1978). Total intravenous nutrition results in some degree of atrophication or wasting of the intestine mucus membrane. Animal experimentation has shown that glutamine is able to counteract this negative effect, when administered intravenously. The atrophication of intestine mucus membrane observed in conjunction with intravenous nutrition, and also in conjunction with serious trauma, can contribute to the passage of bacteria from the wall of the intestine into the blood, which can have a decisive influence on the ability of the patient to survive. The administration of glutamine to animals suffering from experimentally induced bowel damage has been found to result in a lower mortality rate (Hwang, T.L., et al: Preservation of Small Bowel Mucosa Using Glutamine-Enriched Parenteral Nutrition. Surg. Forum 37:56-58 (1986).

An optimal treatment with the intention of maintaining normal bowel wall function would therefore seem to require the administration of considerable quantities of glutamine, for example in the case of serious trauma, sepsis and burns, for patients treated with cytostatic or radioactive radiation, and also in the case of inflammatory diseases, such as morbus Chron or ulcerative colitis.

A nutrient solution which contains glutamine together with other nutritious substances is highly desirable. The problem with such solutions, however, is that solutions which contain glutamine cannot be sterilized by autoclaving, since free glutamine in solution is not heat resistant. When a solution which contains glutamine is heated or stored for long periods of time at room temperature, the glutamine will decompose to ammonia and pyroglutamic acid. Such substances are unacceptable in nutrient solutions intended for intravenous administration. Consequently, present-day commercially available parenteral nutrient amino acid solutions contain no glutamine.

Alpha-keto-glutarate (AKG) is active in various transamination reactions and thereby adopts a central roll in the amino acid metabolism. It has long been known that glutamine can be formed from AKG via glutamic acid. It has also been found that when administered intravenously, AKG is able to counteract the depletion of the free content of glutamine intracellular in muscle after operative trauma (Wernerman, et al, The Lancet 335, No. 8691, 701-703, 1990). This indicates that AKG could be used as a glutamine precursor in an intravenous nutrient supply or support.

Wilmore (WO 87/01587) discloses the use of glutamine in quantities of up to 0.2-3 g/kg of body weight and day in conjunction with trauma.

Veech (WO 87/03806) utilizes glutamine, optionally in mixture with AKG in small quantities, to influence the redox system.

Vinnars (EP 0 318 446) discloses the composition of a posttraumatic solution treatment. Although based on a conventional amino acid mixture, this composition is characterized in that it also includes 5-30 g glutamine and/or 5-25 g AKG per litre, and optional L-asparagine and acetoacetate.

It has been found that peptide-bound glutamine, e.g. glycyl-L-glutamine and also L-alanyl-L-glutamine are acceptably stable when subjected to heat treatment in solution; it has also been found that these substances are biologically active as a glutamine source. This also applies to N-acetyl-L-glutamine. Fürst, et al (DE 3206 784) discloses an amino acid solution which is characterized in that it contains glutamine in the form of water-soluble dipeptides or tripeptides.

Adibi (BE-887941) discloses an aqueous solution which contains at least two dipeptides or tripeptides having a single glycine molecule as the N-terminal amino acid.

Magnusson, et al (SE 8703567-1) discloses an amino acid solution which is characterized in that it contains 2-30 g of N-acetyl-L-glutamine per litre of solution.

Problems

Nutrient solutions for parenteral administration (Large Volume Parenterals) are normally sterilized at about 121°C for 15 minutes, in accordance with standardized techniques. When the solutions contain components that are able to react with one another or which become unstable when subjected to heat, it is not, however, possible to follow the standardized procedures. Thus, none of the commercially available amino acid solutions contains glutamine.

Our earlier patent application, SE 8902544-9, discloses a method of solving the problem of the instability of glutamine, this solution involving the sterilization of powdered glutamine by ionizing radiation prior to mixing the glutamine with the remaining components in the nutrient solution.

It is also conceivable to freeze-dry a sterile filtered glutamine solution and to dissolve the freeze-dried powder aseptically in conjunction with its use. However, because glutamine is not readily dissolvable, the dissolution of glutamine requires the use of large volumes of liquid, which renders the freeze-drying process considerably expensive. Since it is necessary to dissolve the freeze-dried glutamine in corresponding volumes of liquid, this method would also necessitate administering large quantities of liquid to the patient, which is not possible or feasible in many instances. For example, the administration of 60 grams of L-glutamine would require a liquid volume in excess of 2 litres.

A third possibility is to supply the glutamine in the form of a precursor which can be converted at least

partially to glutamine in the body.

It is impossible, however, to administer large quantities of AKG, in view of the resultant pH-values (very low), among other things. Neither is it possible to administer large quantities of AKG in the form of sodium or calcium salt, in view of the non-physiological load represented by these mineral substances. Correspondingly, the administration of large quantities of the neutral ornithine salt of the alpha-keto-glutarate would subject the body to an unreasonable quantity of ornithine.

A fourth possibility is one of administering glutamine in the form of a derivative, preferably in the form of a dipeptide. However, when it is necessary to administer glutamine in large quantities, the other amino acid in the dipeptide, preferably glycine or alanine, will also be present in large quantities. (A daily dosage of 60 g glutamine corresponds, e.g., to 37 grams of alanine, alternatively 31 grams of glycine, depending on whether the supply is effected in the form of the alanyl-peptide or the glycyl-peptide). From the physiological aspect, this implies unfavourable quantities of glycine or alanine. When supplying the glutamine peptide to a commercial amino acid solution, the peptide-bound alanine or the peptide-bound glycine is also added to corresponding free amino acid in the solution, and the patient is thereby liable to obtain a negative imbalance in the amino acid conversion.

Furthermore, a supply of 80-90 g of a dipeptide would be likely to exceed the ability of the organism to cleave (hydrolyze) the peptide in order to release l-glutamine. This would result in a drastic increase in plasma levels of the peptide, pronounced secretion of the unconsumed

peptide in the urine and therewith poor use of the peptide administered.

Furthermore, when in solution the dipeptides in question are, in many cases, not completely stable during the sterilizing process or when stored for long periods of time at room temperature. Consequently, the dipeptide solution must be subjected to comprehensive analytical and biological processes in order to ensure the quality of the peptide solutions from a technical and toxicological aspect.

Furthermore, the price per unit of glutamine based on a glutamine peptide is about 10-20 times higher than the price of a corresponding quantity of pure L-glutamine.

The proposed invention enables large quantities of glutamine to be administered without interference from the aforediscussed problems concerning technical instability, large volumes when dissolving and administering glutamine, and, particularly with respect to peptide supply, high costs, metabolic imbalances and physiological overloads.

Detailed description of the invention

The invention relates to a preparation for oral or parenteral use, characterized in that the preparation includes free L-glutamine and also at least one L-glutamine derivative and optionally at least one L-glutamine precursor, said preparation being prepared aseptically and freeze-dried; in that the preparation is in powder form and is radiation sterilized, or is in the form of a solution which is stored at low temperature, preferably in a frozen state. By low temperature is meant a temperature lower than room temperature, and

preferably a temperature within the range of 2-8°C.

The derivative preferably consists of peptides, such as glycyl-L-glutamine and/or L-alanyl-L-glutamine, and the precursor may consist of alpha-keto-glutaric acid or the salt/derivative thereof. The derivative may also consist of N-acetyl-L-glutamine.

In addition to containing L-glutamine and at least one derivative of L-glutamine and/or a precursor to L-glutamine, the preparation may also contain other nutrient components, alternatively technical auxiliary substances, such as carbohydrates, sugar alcohols, vitamins and/or amino acids, preferably in freeze-dried form.

The present invention also relates to a nutrient solution which contains the aforedescribed preparation and further amino acids, fat emulsion, energy substrate, such as glucose, sugar alcohols and keto-acids, vitamins, electrolytes and/or trace elements.

According to one method, the claimed preparation is produced by dissolving the preparation components, sterile filtering the solution and thereafter freeze-drying the sterile solution.

According to an alternative method, the components are mixed together in powder form and the resultant mixture is then sterilized by radiation.

According to another alternative, the preparation components are mixed in solution and the solution is sterile filtered and stored in a cold or frozen state. It will be understood that the preparation is produced under aseptic conditions.

The invention also relates to a method of preparing a nutrient solution, which comprises the steps of transferring a solution of amino acids, fat emulsion and/or energy substrate to the glutamine preparation, said solution being enclosed in a container which is placed under a pressure that is higher than the pressure over the preparation. An alternative method of preparing this nutrient solution is characterized by enclosing a solution of amino acids, fat emulsion and/or energy substrate in a container which is placed under a pressure that is lower than atmospheric pressure, and by reconstituting the glutamine preparation and transferring said reconstituted preparation to said solution under the influence of a pressure which is greater than the pressure over the solution.

A conceivable alternative to the aforedescribed embodiments of the preparation is to pour the sterile-filtered solution containing free glutamine and at least one glutamine derivative/glutamine precursor into an appropriate container, freezing the container and its contents, delivering said container to the destination and storing the container in a frozen state (at about -20°C) until the time of its use. Alternatively, the solution can be stored in cold conditions (+2°C to +8°C) over a shorter period of time.

The final parenteral nutrient solution can be prepared in accordance with any one of a number of different methods, the method chosen depending on the chosen form of the inventive preparation and on which other components shall be present in the final nutrient solution. A number of examples of different methods of producing the inventive preparation are described below. These examples take their starting point from an inventive preparation of a freeze-dried powder, which is the

alternative of most interest from a commercial and handling aspect. When the third alternative method of preparing the preparation is chosen (solution/deep-frozen solution of free glutamine and at least one glutamine derivative), it is, of course, possible to use the solution directly, subsequent to bringing the solution to a suitable temperature.

In the case of partial nutrient therapy, it is often desired to administer a main component, this component normally being contained in a single package or dosage unit. For example, it is possible to administer a glucose solution, or to administer an amino acid solution in order to improve the patient's nitrogen balance. When wishing to also administer glutamine, the freeze-dried preparation can be dissolved in a part of the aforesaid solution. The transfer of liquid between the containers can be effected by creating a partial vacuum in the receiving container (see the following).

An advantage can be gained in this case, when significant quantities of nutrient components are already present in the freeze-dried preparation.

It is often desired to administer the patient with a more complete nutrient mixture that contains glutamine. In this case, the technique of transferring solution from one container to another with the aid of a partial vacuum can be beneficially applied.

In this case, there is preferably transferred to the inventive preparation of freeze-dried glutamine a concentrated glucose solution, alternatively an amino acid solution or a fat emulsion, with the inventive preparation placed under a partial vacuum. Subsequent to dissolution of the freeze-dried substances and

equalization of the pressure in the container, this solution can be transferred, in turn, to the glucose/amino acid/solution or to the fat emulsion present in an incompletely filled container under vacuum. In this way, there is obtained a nutrient solution which contains several significant nutrient components that can be administered to the patient from one single package, which affords important advantages in practice.

When it is desired to administer to a patient a solution that contains all the necessary nutrient components, these components can be supplied by simultaneous or consecutive infusion from different bottles or other container types.

It is often preferred to administer a complete mixture of nutrient components from one single container (normally a 3-litre plastic container). However, it is necessary to prepare such a mixture regularly from individual nutrient solutions at the time of use, or is obtained from the supplier in the form of a prepared mixture. An inventive glutamine preparation is also used in these cases to produce a glutamine-containing nutrient solution, which is then transferred to the mixing container.

The present invention involves the aforediscussed problems concerning large volumes, high costs, metabolic imbalances and the necessity of carrying out comprehensive analytical and biological processes, and provides a nutrient solution which fulfils all requirements with respect to variation, sterility, stability and nutritional balance.

Because the solution contains both free, natural L-glutamine and one or more glutamine-containing peptides

and/or metabolic precursors to glutamine, it is possible to obtain sufficiently high quantities of glutamine without supplying unfavourable quantities of either peptide or other amino acids in the peptide, for example glycine and alanine, and without the volumes supplied or the resulting costs being unrealistic.

Because the preparation may also contain other nutrient components, such as amino acids, carbohydrates, vitamins, etc., the costs represented by the freeze-drying process can be carried by/shared among the various components. When the solution is prepared under the aforedescribed conditions and stored in a freeze-dried state, all problems relating to instability when preparing the preparation and during the storage thereof are avoided.

Completely new possibilities for complete nutrient therapy capable of being adapted to the needs of each individual patient are achieved by combining the freeze-dried material with different nutrient solutions according to the disclosures set forth in the following Examples 1-11.

Corresponding advantages are also achieved when the mixture of glutamine components is radiation sterilized or prepared aseptically and deep-freezed.

Examples

The following named products from KABI Nutrition AB, Stockholm, were used in the Examples.

- Vamin®14 EF, Vamin®18 EF, and Vamin®9 Glucose are concentrated amino acid solutions.

- Intralipid® is a 20% fat emulsion for intravenous nutrient supply.
- Addamel® is an additive solution with electrolytes and trace elements.
- Addiphos® is an additive solution with phosphate.
- Soluvit® is a mixture of water-soluble vitamins.
- Vitalipid® is an additive solution in emulsion form, containing fat-soluble vitamins.
- KABI Bag® is a 3-litre mixing bag by means of which a complete nutrient mixture can be administered to the patient.

**Example 1**

A solution was prepared by dissolving 7.5 g of L-glutamine, 14.0 g of glycyl-L-glutamine, and 5.0 g of alanyl-L-glutamine in a total volume of 250 ml of distilled, pyrogen-free water.

The solution was sterile-filtered and poured into a 1-litre bottle under aseptic conditions. The solution was then frozen and freeze-dried under aseptic conditions, whereafter the bottle was sealed in the freeze drier prior to interrupting the vacuum.

Prior to use, the freeze-dried solution was reconstituted, by adding 500 ml of Vamin 18 EF®. This transfer was effected by placing the freeze-dried glutamine under partial vacuum and drawing the Vamin to the glutamine by suction with the aid of a transfer device constructed herefor.

This example provides a complete amino acid solution containing glutamine, which satisfies basal amino acid requirements.

Example 2

A solution was prepared by dissolving 7 g of L-glutamine 10.0 g of glycyl-L-glutamine and 10.0 g of alpha- keto-glutarate (the monosodium salt) in a total volume of 250 ml of distilled, pyrogen-free water.

The solution was sterile filtered and poured into a 1-litre bottle under aseptic conditions. The solution was then frozen and freeze-dried under aseptic conditions. The bottle was sealed in the freeze-drier, prior to interrupting the vacuum.

Prior to use, the freeze-dried solution was reconstituted by adding 500 ml of Vamin 18 EF®. The transfer of Vamin to the freeze-dried solution was effected by placing the glutamine under a partial vacuum and drawing the Vamine to the glutamine by suction with the aid of a transfer device constructed herefor.

Example 3

A solution was prepared by mixing 4 g of L-glutamine, 10.0 g of glycyl-L-glutamine, 8.0 g of alanyl-L-glutamine and 8.0 g of alpha-keto-glutarate (as the ornithine salt) in a total volume of 250 ml of distilled, pyrogen-free water.

The solution was sterile-filtered and poured into a 1-litre bottle under aseptic conditions.

The solution was then frozen and freeze-dried under aseptic conditions. The bottle was sealed in the freeze drier, prior to interrupting the vacuum. Prior to use, the freeze-dried solution was reconstituted by adding 500 ml of a 20%-glucose solution. The transfer of the

glucose solution to the freeze-dried solution was effected by placing the glutamine under a partial vacuum and drawing the solution to the glutamine by suction with the aid of a transfer device constructed herefor.

**Example 4**

A solution was prepared by dissolving 6 g of L-glutamine, 10 g of glycyl-L-glutamine and 10 g of alpha-ketoglutarate (as the arginine salt) in a total volume of 300 ml of distilled, pyrogen-free water. The remainder of the preparation process was effected in accordance with Example 3 above.

**Example 5**

A solution was prepared by dissolving 9.0 g of L-glutamine, 14.0 g of glycyl-L-glutamine, 9.0 g of alanyl-L-glutamine and 50 g of glucose in a total volume of 250 ml of distilled, pyrogen-free water.

The solution was sterile-filtered and poured into a 1-litre bottle under aseptic conditions.

The solution was frozen and freeze-dried under aseptic conditions. The bottle was sealed in the freeze-drier, prior to interrupting the vacuum.

Prior to use, the freeze-dried solution was reconstituted by adding 500 ml of Vamin 14 EF®. The transfer of Vamin to the freeze-dried solution was effected by placing the glutamine under a partial vacuum and drawing the Vamine to the glutamine by suction with the aid of a transfer device constructed herefor. An ampull containing Addamel N® (10 ml) was added to the solution obtained.

This example provided a complete amino acid solution, containing glutamine, which covers low requirements of amino acids, glucose and trace substances.

**Example 6**

A solution was prepared by dissolving 7.0 g of L-glutamine, 18.0 g of glycyl-L-glutamine, 15.0 g of alanyl-L-glutamine and 100 g of glucose in a total volume of 300 ml distilled, pyrogen-free water.

The solution was sterile-filtered and poured into a 1-litre bottle under aseptic conditions. The solution was frozen and freeze-dried under aseptic conditions. The bottle was sealed in the freeze drier, prior to interrupting the vacuum.

Prior to use, the freeze-dried solution was reconstituted by adding at least 500 ml of Vamin 9 Glucose® taken from a 1000 ml-bottle. The transfer of Vamin to the freeze-dried solution was effected by placing the glutamine under a partial vacuum and drawing the Vamine to the glutamine by suction with the aid of a transfer device constructed herefor. The reconstituted solution and any residue of the Vamin 9 solution was transferred to a 3-litre mixing bag of the KABI Bag type.

500 ml Intralipid® 20% were then added to the mixing bag. Appropriate trace elements, electrolytes, water-soluble and fat-soluble vitamins, in the form of preparations Addamel, Addiphos, Soluvit and Vitalipid, were added to the amino acid solution or to the fat emulsion prior to mixing in the KABI Bag.

The procedure described in this example enables a complete nutrient solution containing glutamine to be

obtained in a simple fashion.

**Example 7**

A solution was prepared by dissolving 2.7 g of L-glutamine, 20.0 g of glycyl-L-glutamine and 11.8 g of alanyl-L-glutamine in 100 ml of sterile, pyrogen-free water. The solution was sterile-filtered and poured aseptically into a sterile 100 ml glass bottle. The solution was cooled and stored at a temperature of +2°C to +8°C up to its time of use, within 7 days.

**Example 8**

A solution was prepared by dissolving 2.7 g of L-glutamine, 20.0 g of glycyl-L-glutamine and 11.8 g of alanyl-L-glutamine in 100 ml of sterile, pyrogen-free water. The solution was sterile-filtered and poured aseptically into a sterile 100 ml plastic container. The solution was frozen and stored at a temperature of about -18°C. Prior to use, the solution was thawed at a temperature of at most +40°C, prior to being administered as an infusion, or prior to being included in a mixture of nutrient solutions.

**Example 9**

A powder mixture was introduced into a 3-litre plastic container of the KABI Bag® type. The mixture contained 40 g of L-glutamine and 10 g of alpha-keto-glutarate. The plastic container was then sealed and radiation-sterilized with a radiation dosage of 25 kiloGray.

Prior to use, nutrient solutions were introduced to the container in accordance with the following program, such as to obtain a fully balanced nutrient solution for

patient administration. 750 ml of Intralipid® 20%, 1000 ml of Vamin 14 EF, 1000 ml of glucose solution (30%) and appropriate trace elements, electrolytes, water-soluble and fat-soluble vitamins in the form of the preparations Addamel, Addiphos, Soluvit and Vitalipid, were added introduced into the mixing bag. (Were added to the amino acid solution or the fat emulsion prior to mixing in the KABI Bag).

**Example 10**

A powder mixture was introduced into a 200 ml plastic container which included suitable ports for aseptic solution supply and solution tapping purposes. The mixture contained 5 g of L-glutamine and 20 g of glycyl-L-glutamine. The plastic container was sealed and then radiation sterilized with a radiation dosage of 25 kiloGray.

Prior to use, 200 ml of sterile water were introduced into the container.

This example provides a concentrated additive solution of glutamine.

**Example 11**

A solution was prepared by dissolving 7.0 g of L-glutamine, 20.0 g of glycyl-L-glutamine, 12.8 g of alanyl-L-glutamine, 1.05 g of L-isoleucine, 1.50 g of L-leucine, 1.70 g of L-lysine, 1.05 g of L-methionine, 0.10 g of L-cysteine, 1.50 g of L-phenyl alanine, 0.04 g of L-thryosine, 1.05 g of L-threonine, 0.35 g of L-tryptophan, 1.38 g of L-valine, 3.00 g of L-alanine, 2.10 g of L-arginine, 0.63 g of L-asparaginic acid, 1.05 g of L-glutamic acid, 1.30 g of L-histidine, 1.30 g of

L-proline, 0.85 g of L-serine, 1.50 g of glycine, and 50 g of glucose in a total volume of 350 ml of distilled, pyrogen-free water.

The solution was sterile-filtered and poured into a 1-litre bottle under aseptic conditions.

The solution was frozen and freeze-dried under aseptic conditions. The bottle was sealed in the freeze drier prior to interrupting the vacuum. Prior to use, the freeze-dried solution was reconstituted by adding 500 ml of a 10%-glucose solution. The transfer of the glucose solution to the freeze-dried solution was effected by placing the glutamine under a partial vacuum and drawing the solution to the glutamine by suction with the aid of a transfer device constructed herefor.

## CLAIMS

1. A composition for oral or parenteral use, characterized in that the composition contains free L-glutamine and also at least one derivate of L-glutamine and optionally at least one precursor to L-glutamine.

2. A composition according to claim 1, characterized in that said composition is prepared aseptically and freeze-dried.

3. A composition according to claim 1 characterized in that said composition is in powder form and is radiation sterilized.

4. A composition according to claim 1, characterized in that said composition is in the form of a solution which is stored at low temperature, preferably in a deep-frozen form.

5. A composition according to any one of Claims 1-4, characterized in that the derivative consists of peptides, preferably glycyl-L-glutamine and/or L-alanyl-L-glutamine.

6. A composition according to any one of Claims 1-4, characterized in that the derivative is N-acetyl-L-glutamine.

7. A composition according to any one of Claims 1-4, characterized in that the precursor is alpha-keto-glutaric acid or a salt/derivative thereof.

8. A composition according to any one of the preceding Claims, characterized in that the composi-

tion contains other nutrient components, such as carbohydrates, sugar alcohols, vitamins and/or amino acids, in addition to L-glutamine and at least one derivative of L-glutamine and/or at least one precursor to L-glutamine.

9. A composition according to Claim 8, c h a r a c t e r i z e d in that it is freeze-dried.

10. A nutrient solution, c h a r a c t e r i z e d in that the solution contains the composition according to any one of the preceding Claims, together with additional amino acids, fat emulsions, energy substrates, such as glucose, sugar alcohols and keto-acids, vitamins, electrolytes and/or trace elements.

11. A method of producing a composition according to Claim 2 or Claim 8, c h a r a c t e r i z e d by dissolving the components, sterile-filtering the solution and thereafter freeze-drying the sterile solution.

11. A method of producing a composition according to Claim 3 or Claim 8, c h a r a c t e r i z e d by mixing the components in powder form and radiation-sterilizing the resultant mixture.

12. A method of producing a composition according to Claim 4 or Claim 8, c h a r a c t e r i z e d by mixing the components in solution, sterile-filtering the solution and storing the solution under cold conditions or deep-freezing the solution.

14. A method of producing a nutrient solution according to Claim 10, c h a r a c t e r i z e d by transferring a solution of amino acids, fat emulsion and/or energy substrate to the composition according to any one of

Claims 1-4 or according to Claim 8, said solution being enclosed in a container which is placed under a pressure that is higher than the pressure maintained over the composition.

15. A method of producing a nutrient solution according to Claim 10, c h a r a c t e r i z e d by enclosing a solution of amino acids, fat emulsion and/or energy substrate in a container which is placed under a pressure that is lower than atmospheric pressure, and by transferring the composition according to any one of Claims 1-4 or according to Claim 8, optionally in dissolved form, to said solution under the influence of a pressure which is higher than the pressure maintained over the solution.

# INTERNATIONAL SEARCH REPORT

International Application No PCT/SE 91/00810

## I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all)[6]

According to International Patent Classification (IPC) or to both National Classification and IPC

IPC5: A 61 K 31/195, 37/02, A 23 L 1/305

## II. FIELDS SEARCHED

Minimum Documentation Searched[7]

| Classification System | Classification Symbols |
|---|---|
| IPC5 | A 61 K; A 23 L |

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in Fields Searched[8]

SE,DK,FI,NO classes as above

## III. DOCUMENTS CONSIDERED TO BE RELEVANT[9]

| Category * | Citation of Document,[11] with indication, where appropriate, of the relevant passages[12] | Relevant to Claim No.[13] |
|---|---|---|
| X | WO, A1, 8903688 (AB ERIK VINNARS)<br>5 May 1989,<br>see the whole document<br>-- | 1-15 |
| X | WO, A1, 8703806 (RICHARD L. VEECH)<br>2 July 1987,<br>see the whole document<br>-- | 1-15 |
| X | DE, A1, 2529935 (DR. EDUARD FRESENIUS, CHEMISCH-PHARMAZEUTISCHE INDUSTRIE KG)<br>13 January 1977,<br>see the whole document<br>-- | 1-10 |
| X | WO, A1, 8701589 (BRIGHAM AND WOMEN'S HOSPITAL)<br>26 March 1987,<br>see the whole document<br>-- | 1-15 |

* Special categories of cited documents:[10]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

## IV. CERTIFICATION

| Date of the Actual Completion of the International Search | Date of Mailing of this International Search Report |
|---|---|
| 10th March 1992 | 1992 -03- 16 |
| **International Searching Authority** | **Signature of Authorized Officer** |
| SWEDISH PATENT OFFICE | Gunilla Claesson<br>Gunilla Claesson |

Form PCT/ISA/210 (second sheet) (January 1985)

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)

| Category * | Citation of Document, with indication, where appropriate, of the relevant passages | Relevant to Claim No |
|---|---|---|
| P,X | WO, A1, 9116067 (RESEARCH CORPORATION TECHNOLOGIES, INC.) 31 October 1991, see the whole document -- | 1-15 |
| P,X | WO, A1, 9101135 (KABIVITRUM AB) 7 February 1991, see the whole document -- | 1-15 |

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FURTHER INFORMATION CONTINUED FROM THE SECOND SHEET

V. [X] OBSERVATIONS WHERE CERTAIN CLAIMS WERE FOUND UNSEARCHABLE [1]

This international search report has not been established in respect of certain claims under Article 17(2) (a) for the following reasons:

1. [ ] Claim numbers....., because they relate to subject matter not required to be searched by this Authority, namely:

2. [X] Claim numbers 1-4, 8-15, because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

See next sheet.

3. [ ] Claim numbers....., because they are dependent claims and are not drafted in accordance with the second and third sentences of PCT Rule 6.4(a).

VI. [ ] OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING [2]

This International Searching Authority found multiple inventions in this international application as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims of the international application.

2. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims of the international application for which fees were paid, specifically claims:

3. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the the claims. It is covered by claim numbers:

4. [ ] As all searchable claims could be searched without effort justifying an additional fee, the International Searching Authority did not invite payment of any additonal fee.

Remark on Protest

[ ] The additional search fees were accompanied by applicant's protest.

[ ] No protest accompanied the payment of additional seach fees.

FURTHER INFORMATION CONTINUED

The wordings "derivate of L-glutamine" and "precursor to L-glutamine" in claim 1 are too broadly formulated to permit an adequate search. The search has therefore essentially been restricted to compositions containing the compounds specifically mentioned in claims 5-7 and the examples. (See PCT Art. 6).

# ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO.PCT/SE 91/00810

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the Swedish Patent Office EDP file on 01/02/92
The Swedish Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

| Patent document cited in search report | Publication date | Patent family member(s) | | Publication date |
|---|---|---|---|---|
| WO-A1- 8903688 | 89-05-05 | AU-D- | 2623888 | 89-05-23 |
| | | EP-A- | 0318446 | 89-05-31 |
| | | EP-A- | 0398879 | 90-11-28 |
| | | JP-T- | 3500775 | 91-02-21 |
| WO-A1- 8703806 | 87-07-02 | AU-D- | 6777487 | 87-07-15 |
| | | EP-A- | 0250559 | 88-01-07 |
| DE-A1- 2529935 | 77-01-13 | FR-A-B- | 2337510 | 77-08-05 |
| WO-A1- 8701589 | 87-03-26 | AU-B- | 599335 | 90-07-19 |
| | | AU-D- | 6337886 | 87-04-07 |
| | | EP-A- | 0238553 | 87-09-30 |
| | | JP-T- | 63501214 | 88-05-12 |
| | | US-A- | 4857555 | 89-08-15 |
| | | US-A- | 5039704 | 91-08-13 |
| WO-A1- 9116067 | 91-10-31 | NONE | | |
| WO-A1- 9101135 | 91-02-07 | EP-A- | 0434820 | 91-07-03 |
| | | SE-A- | 8902544 | 91-01-18 |